

Comparison of Hypertonic Saline Solutions and Dextran in Dialysis-Induced Hypotension¹

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ABSTRACT

The efficacy of three hypertonic saline solutions for treating dialysis-induced hypotension in a randomized, blinded, crossover clinical trial of 10 patients (a minimum of three cycles per solution) was compared. Dialysis-induced hypotension, defined as a decrease in systolic blood pressure of at least 10 mm Hg or systolic blood pressure less than 100 mm Hg, was treated with an iv bolus of either 10 mL of 23% saturated hypertonic saline, 30 mL of 7.5% hypertonic saline, or 30 mL of 7.5% saline with 6% dextran 70, each containing similar osmolar loads of 80, 80, and 100 mosM, respectively. All three solutions raised systolic blood pressure within 5 min (mean pretreatment systolic blood pressure, 87 mm Hg; mean posttreatment systolic blood pressure, 101 mm Hg; $P < 0.05$). The magnitude of the increase was greater with saturated hypertonic saline (15 mm Hg) and dextran 70 (17 mm Hg) compared with that with hypertonic saline (9 mm Hg; $P < 0.05$). At 10 min, dialysis-induced hypotension was less frequent with saturated hypertonic saline (incidence, 9%) com-

pared with hypertonic saline (45%). Beyond 10 min, however, there was a trend toward a lower incidence of further dialysis-induced hypotension with dextran 70. There were no side effects. Given equal osmole loads, the more concentrated solution produced a greater increase in systolic blood pressure. The addition of an oncotic agent such as dextran may prolong the blood pressure response beyond 10 min. It was concluded that hypertonic saline solutions safely and effectively treat dialysis-induced hypotension.

Key Words: Hypotension, dextran, hemodialysis, hypertonic

Dialysis-induced hypotension (DIH) is a common complication among hemodialysis patients that is estimated to occur in up to 50% of dialysis treatments (1) and is associated with a high acute morbidity as well as an adverse effect on the overall quality of life (1,2). The cause of DIH is multifactorial and may include cardiac arrhythmias, decreased cardiac output, autonomic insufficiency, pericardial disease, changes in osmolality, intravascular volume depletion, and the use of an acetate dialysate (3-5). Multiple treatments and changes in the dialysis procedure have been used in the past to prevent or treat this problem. Historically, the treatment for DIH has included noncompliant dialyzers, which were first used in 1965 with the introduction of the hollow fiber kidney (6 [p. 46],7,8). In addition, other methods such as bicarbonate dialysis (9), increased dialysate sodium concentration (10), and isolated ultrafiltration (11) are still being used to decrease dialysis-induced hemodynamic instability. Recently, lysine vasopressin spray has been administered before and during dialysis to decrease the frequency of hypotension during a dialysis treatment (12). Despite these efforts, DIH persists in the dialysis population.

One traditional method used to treat DIH has been the iv injection of hypertonic or hyperoncotic solutions. The various formulations that are currently being used include albumin, mannitol, and hypertonic saline (HS) (6), but the optimal solution has not been established. The ideal formulation would be inexpensive, rapid in onset, prolonged in duration, and associated with no side effects. There has been a trend toward using HS (usually to 50 10 ml of 23.4% NaCl) because of its lower cost compared with the alternatives. HS is also effective for the relief of

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muscle spasm that may accompany episodes of hypotension. However, the effect of HS is often short lived, requiring repeated injections of the solution. Only a paucity of data exists to establish the optimal concentration of the solution. In our study, we compared the effectiveness of various saline solutions with different tonicities but similar osmole loads to determine whether the increased blood pressure response is related to a higher tonicity of the solution or to the overall osmoles infused. We also investigated whether adding dextran to these hypertonic solutions would successfully maintain blood pressure.

METHODS

Patient Selection

After giving informed consent, adult hemodialysis patients from the hemodialysis units of Letterman and Brooke Army Medical Centers were enrolled in the study. Indications for hemodialysis included uremia, intractable volume overload, electrolyte imbalance, drug toxicity, or acidosis. These patients underwent dialysis two or three times per week on GAMBRO AK10 nonvolumetric controlled machines (Cobe, Lakewood, CO). The patients' dialysis prescriptions did not change during the study. They were dialyzed against a 140-mEq/L sodium, 2- to 4-mEq/L potassium, and 35-mEq/L bicarbonate bath. Sodium concentration was not varied during the dialysis. Patients maintained a stable dry weight for 2 wk before entering the study. Predialysis evaluation included a complete history and physical examination, chest x-ray, electrocardiogram, routine chemistries, urinalysis, complete blood cell count, multiple gated acquisition scan, and echocardiogram. Patients were excluded for the following reasons: left ventricular ejection fraction of less than 30% by multiple gated acquisition scan; more than a minimal amount of pericardial fluid by echocardiogram; occult gastrointestinal blood loss as manifested by a history of hematemesis, hematochezia, or a positive stool guaiac test; a serum sodium level of more than 150 mEq/L within the past week. Hypotensive episodes occurring within the last hour of the dialysis treatment were not treated with any test solutions because the effects could not be adequately evaluated. Patients taking antihypertensive or antidepressant medication were asked to withhold these drugs beyond midnight the day before dialysis. This study protocol was approved by the institutional review boards of both medical centers, and Food and Drug Administration approval was obtained for the use of 7.5% NaCl with 6% dextran 70.

Patient Assignments

To eliminate the sequence effect caused by the sequence in which a solution is given, each patient

was assigned to one of six treatment groups. Only one test solution was administered to a patient during a single dialysis session. Six sequences were necessary to cover every possible permutation of the three study solutions (Table 1).

Treatment Protocol

During the study period, serum electrolytes were measured weekly on either Wednesday or Thursday after dialysis. During each dialysis session, blood pressure and pulse were monitored at least every 30 min with an automatic recording device (Dinamap; Critikon Corp, Marietta, GA). The baseline blood pressure measurement was obtained 5 min after dialysis was begun. Hypotension was defined as systolic blood pressure (SBP) less than 100 mm Hg or a decrease in the SBP of at least 10 mm Hg if the baseline SBP was already less than 100 mm Hg.

When hypotension occurred, the patient received an iv infusion of the test solution according to the sequence assigned to the patient for that treatment. The blood pressure and pulse response were subsequently measured every 5 min. A successful response was defined as an increase in SBP of at least 10 mm Hg or SBP greater than 100 mm Hg. If a successful response was not achieved after 10 min, another dose of the same test solution was given. If a response was still not observed 10 min after the second infusion, standard measures of dialysis resuscitation were instituted, including saline, albumin, mannitol, an attempt to decrease transmembrane pressure, or termination of dialysis. Only one study solution was used on a particular patient in a given day. During the next dialysis session, the next study solution in sequence was used in the above fashion. The goal was to allow each patient to complete at least three cycles of the assigned solution sequence. If hypotension did not occur during a particular dialysis session, the assigned solution was not skipped but, rather, was administered during the next episode of DIH.

TABLE 1. Sequence of each treatment group^a

Group	Solution Sequence
1	ABC
2	ACB
3	BAC
4	BCA
5	CAB
6	CBA

^a Solution A, 10 mL of 23% NaCl (SHS); Solution B, 30 mL of 7.5% NaCl (HS); Solution C, 30 mL of 7.5% NaCl with 6% dextran 70 (HSD).

Statistical Methods

SBP and pulse measurements before and after the first injection of test solution were statistically analyzed, with the baseline measurement used as a covariate. An analysis of variance model was used to determine any differences between the three solutions, which included the factors of solution and sequence. Differences between individual means were tested by the Neuman-Keuls procedure when appropriate. The proportion of second injections of any one solution was analyzed by the use of nonparametric techniques. The level of significance was defined at 0.05.

RESULTS

Patient Profile

A total of 19 dialysis patients were entered into the study, but 9 were excluded from statistical analysis because they did not complete the requisite three cycles of each test solution over the 9-month study period. Of the 10 remaining patients, 7 (70%) were men. The average age of our patients was 69 yr (range, 62 to 73), and all had a history of hypertension. One patient had a history of such a high frequency of DIH that he was routinely premedicated with iv ephedrine before each dialysis treatment; this routine was not altered during the study period. No unanticipated delays or interruptions occurred in the routine dialysis treatments for any of the patients during the study period. Approximately 2 months into the study, our dialysis units acquired recombinant erythropoietin (Epoen; Amgen, Thousand Oaks, CA) and began using it for patients who fit the criteria of anemia due to chronic renal disease. All 19 patients in our study received erythropoietin.

Solution Effect

Mean SBP during dialysis are presented in Table 2. The average level of hypotension before a test solution was given was SBP of 87 ± 7 mm Hg. Five

TABLE 2. Response to hypertonic solutions^a

	Baseline	Before Solution (mmHg)	5 Min After
SHS	122 ± 19	87 ± 7	102 ± 7 ^{bc}
HS	123 ± 22	89 ± 7	98 ± 9 ^b
HSD	131 ± 29	85 ± 8	102 ± 8 ^{bc}

^a Values are mean SBP ± SD.

^b $P < 0.05$ compared with before solution.

^c $P < 0.05$ compared with HS.

minutes after the initial bolus, all three solutions resulted in a statistically significant elevation in SBP compared with the pretreatment values. In addition, both saturated HS (SHS) and HS with dextran (HSD) provided a greater augmentation of the SBP than did HS at 5 min (102 ± 7 and 102 ± 8 mm Hg versus 98 ± 9 mm Hg; $P < 0.05$). There were no significant differences in reported symptoms within the three groups during that time.

Ten minutes after the initial bolus, patients who still had hypotension were given a second dose of the test solution. The results of this intervention are shown in Table 3. Patients who received SHS initially were significantly less likely to require a repeated injection compared with those who were given HS (9 ± 14 vs $45 \pm 30\%$, $P < 0.05$). The trend was similar, although not statistically significant, for patients who received HSD; $26 \pm 22\%$ required a second injection.

When the blood pressure response was monitored beyond 10 min, $49 \pm 9\%$ of patients who initially received HSD had further episodes of hypotension, compared with $56 \pm 9\%$ and $59 \pm 19\%$ of those who were given SHS and HS, respectively. This trend was not statistically significant.

Sequence Effect

No significant difference was found in the groups of patients given the three solutions in varying sequences. All six groups had similar frequencies of hypotension and blood pressure responses to the test solutions.

Side Effects

In general, all three test solutions were very well tolerated with little or no side effects and no increase in interdialytic weight gain. One patient developed a transient sensation of abdominal bloating a few minutes after receiving a dose of HS and also noted the symptom again several hours after the solution was given. This symptom was felt to be causally unrelated to the test solution. No episodes of nausea, acute mental status changes, seizures, or pulmonary

TABLE 3. Subsequent hypotension after HS

	Episodes at 10 min (%)	DIH After 10 min (%)
SHS	9 ± 14 ^a	56 ± 9
HS	45 ± 30	59 ± 19
HSD	26 ± 22	49 ± 9

^a Denotes $P < 0.05$ compared with HS.

edema were reported in patients given any of the three HS solutions, and no clinical evidence of coagulopathy or anaphylaxis was found in those who received the solution containing dextran. Weekly monitoring of serum sodium revealed seven episodes (incidence, 2%) of hypernatremia (range, 145 to 148 mEq/L). All of these patients were asymptomatic.

DISCUSSION

Overall, we were surprised by the infrequency of DIH seen in our study. Previously, the incidence of DIH was believed to be 25 to 50% (5), but we found the incidence to be closer to 10%, despite the 62- to 73-yr age range of our patient population. As stated earlier, we began using recombinant erythropoietin in all of our dialysis patients during this study; this drug is known to cause an elevation in blood pressure as a side effect, which perhaps may have mitigated the number of hypotensive events. This should not have changed the effect of HS used to treat bona fide episodes of hypotension, however.

HS solutions quickly and effectively raised SBP during episodes of DIH by an average of 9 mm Hg for 7.5% NaCl and 16 mm Hg for both 23% NaCl and 7.5% NaCl with 6% dextran 70. The 5-min responses to the three test solutions are both statistically significant as well as clinically useful, considering that the average pretreatment SBP of 87 mm Hg was low enough to provoke symptoms. The mechanism by which HS immediately raises blood pressure is poorly understood. One possible explanation may be the shift of intracellular fluid into the extracellular and intravascular space caused by the intravascular delivery of additional solute. However, this theory conflicts with the results of Velasco *et al.* (13), who found no appreciable plasma volume expansion for at least 12 h after the administration of HS in a hemorrhage model using anesthetized dogs. They did, however, show a concomitant rise in cardiac inotropy, which may possibly explain the effects of HS.

It is interesting to compare the effects of SHS and HS, both of which contain exactly the same total osmole loads of 80 mosM in differing tonicities. The SBP response to SHS was significantly greater than that to HS, implying that the solution with the higher tonicity provides a greater augmentation of blood pressure. Perhaps the effect of tonicity on positive cardiac inotropy mediates the blood pressure response. Our study did not compare the effects of HS on varying degrees of cardiac left ventricular function.

Of the patients given one or two doses of HS, 40 to 50% remained free of hypotension until the conclusion of the dialysis treatment, suggesting a sustained effect of the initial treatment beyond the first 5 min. We did not, however, compare this treatment with

other modalities used to treat DIH, such as mannitol, albumin, and isotonic crystalloid. On the basis of the study by Holcroft *et al.* in trauma patients (14), we expected that the addition of a colloid agent such as dextran would have helped to prolong the blood pressure response beyond the first few minutes. Our study did show a trend toward fewer episodes of late DIH in patients given the dextran-containing solution. This trend was not statistically significant, which may have been the result of a possible type-2 error, compounded by the relatively few episodes of DIH in our patients who received erythropoietin.

Ours is the first study to formally evaluate the effects of HS solutions in DIH. Although the numbers of patients and episodes of DIH in our study are small, the results indicate the utility of these solutions for this difficult problem encountered in the hemodialysis patient. In conclusion, we found the three formulations of HS tested to be safe, quick, and effective in treating DIH, with the more hypertonic solution providing a greater blood pressure response. The addition of dextran may sustain the effect of HS on increasing blood pressure, but a study involving a larger number of patients is needed to prove this.

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